Haemorrhagic colitis due to *Escherichia coli* O103:H2 associated with infliximab therapy in a patient with rheumatoid arthritis

SIR, A 69-yr old woman had been diagnosed with rheumatoid arthritis (RA) 3 yr ago. She had evidence of active disease despite treatment with prednisolone (12.5–25 mg/day) and methotrexate (12.5 mg/week). As exclusion criteria were absent and informed consent had been obtained, she received a single intravenous infusion of infliximab, a chimeric monoclonal antibody against tumour necrosis factor α (TNF-α). The dose was 200 mg (3 mg/kg). The response was rapid and exceeded 70% improvement from baseline, according to the criteria of the American College of Rheumatology. Methotrexate was continued at the same dosage and prednisolone was reduced to 6.25 mg/day.

Six days later, the patient was admitted to our department with abdominal pain, vomiting and bloody diarrhoea. On physical examination she appeared severely ill. Her body temperature was 38.3°C, her pulse was 110/min and there was diffuse abdominal tenderness without rigidity. Laboratory examination revealed elevated C-reactive protein (92 mg/l) and leucocytosis (13.4 g/l). Sonography showed mural thickening of the entire large bowel. After collection of blood and stool specimens, treatment with intravenous fluids and ciprofloxacin (200 mg twice daily) was started. Stool specimens showed presence of Shiga toxin when screened with Premier-EHEC Elisa (Meridian Diagnostics Inc., Cincinnati, OH, USA). Bacteriological culture yielded sorbitol fermenting enterohaemorrhagic *Escherichia coli* (EHEC) O103:H2, positive for the virulence genes *stx*, *eae* and *hly*. A detailed history of food consumed by the patient during the 5 days before onset of illness was taken, but no vehicle of transmission could be identified definitely. No other members of her household presented any symptoms. By 9 days of hospitalization the patient had recovered fully. Haemolytic-uraemic syndrome (HUS) was not observed during follow-up. Due to the excellent response of her RA, the patient decided to continue treatment with infliximab. The second and third infusions of infliximab were given 8 and 16 weeks later, respectively. Therapy was efficacious and no further infectious complications occurred. Continuation of infliximab is intended.

TNF-α plays a central role in the pathogenesis of RA and Crohn’s disease [1]. Several trials have provided evidence that the anti-TNF-α antibody infliximab reduces disease activity in patients with these conditions [2, 3]. Infliximab is well-tolerated in most cases, however, but there is some concern about its safety profile regarding the occurrence of cancer and serious infections. Upper respiratory tract infections were observed more frequently in patients receiving infliximab compared with those receiving placebo [4]. There are recent data about the possibility of manifestation or reactivation of tuberculosis in patients treated with infliximab [5]. Recently, a patient with invasive pulmonary aspergillosis and lethal outcome in association with infliximab therapy was reported [6]. To our knowledge, this case represents the first report of haemorrhagic colitis due to *E. coli* O103 associated with infliximab therapy.

EHEC has been documented as the cause of haemorrhagic colitis. This organism produces Shiga toxins,
which contribute substantially to disease pathogenesis and complications. O157 is by far the most frequent serotype isolated from patients with EHEC associated diarrhoea. Nevertheless, in Austria, as in Germany, more than half of the cases of diarrhoea-associated HUS are presently due to non-O157 EHEC, \textit{E. coli} O145, O26 and O111 being the most frequently isolated serotypes. Without testing stool specimens for the presence of Shiga toxin, most of these non-O157 EHEC would be missed.

It has been hypothesized that interaction between Shiga toxin and TNF-$\alpha$ may be important in the pathogenesis of HUS. The localized, regulated induction of the proinflammatory cytokine TNF-$\alpha$ in response to infection or tissue damage may result in additional effects, such as increased expression of leucocyte adherence molecules on the vascular endothelium and leucocyte extravasation into tissues [7]. Using a mouse model it was shown that the severity of the disease caused by EHEC could be modified by inhibiting TNF-$\alpha$ [8].

Any causal relationship of therapy with infliximab and subsequent EHEC infection seems speculative and the role of TNF-$\alpha$-inhibition in human HUS is unclear. Patients with RA receiving infliximab should be carefully observed for unusual infectious complications including haemorrhagic colitis due to non-O157 EHEC.


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